DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-526

CV Therapeutics, Inc.
Attention: Ms. Carol Karp
Vice President, Regulatory Affairs
3172 Porter Drive
Palo Alto, CA 94304

Dear Ms. Karp:

Please refer to your new drug application (NDA) dated December 27, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ranexa (ranolazine) 375 and 500 mg Tablets.

We acknowledge receipt of your submissions dated January 10 and 29, February 6, 7, 12, 18, 19, 25, 27 and 28, March 7, 18 (two), 21 (two), and 24, April 2, 3, 4, 8 (two), 11, 15, 28, 29, and 30, May 2, 6, 20, and 23 (two), June 5, 6, 17, and 25, July 1, 17, 22 (two), August 6, 15, and 18 (two), September 5, 6, 9, and 13, and October 7, 10, 20 and 30, 2003.

We have completed our review of your application, as amended, and it is approvable. Approval is contingent on your adequately addressing the deficiencies listed below. Because substantial additional clinical data are needed, no labeling will be included with this letter.

Based on our reviews of the submitted materials, there is evidence that ranolazine is an effective anti-anginal drug in an undifferentiated population of patients, including patients receiving sub-maximal treatment with other anti-anginals. The trials in angina, however, do not adequately characterize the relationship between dose and therapeutic effect sufficiently to provide labeling instructions for its use. Our analyses suggest a relationship of ranolazine concentrations in plasma to clinical effects. However, the great inter-subject variability in these plasma levels and the small number of studies exploring the dose range of ranolazine in patients with angina make it difficult to adequately describe in labeling how ranolazine should be dosed. In study CVT 3033, for instance, doses of 750 mg and 1000 mg were not distinguishable from each other in their effects on exercise tolerance. In study CVT 3031, a crossover design and short treatment period (just one week) were used, and the results suggest that doses of 1000-1500 mg b.i.d. were more effective than a dose of 500 mg BID. It will be necessary to obtain additional dose-response information. In addition, the Agency has three important safety concerns that will need to be addressed prior to approval:

1) Potential testicular toxicity, manifest as impaired fertility in rats in study AT-4136116-R-86-43285-PO-RMF. The available data are inadequate to determine whether this was a chance finding or evidence of testicular toxicity by ranolazine. While no clinical signs of male reproductive toxicity were reported, this is not surprising or reassuring, as adequate assessment of this toxicity typically requires targeted clinical evaluation.

2) Delayed cardiac repolarization, manifest clinically as prolongation of the QT interval. An effect on the QT interval was seen in all patient populations studied, particularly at higher blood concentrations of ranolazine, and you have neither provided sufficient rationale for discounting this as a potential clinical concern nor devised dosing strategies that would avoid significant QT prolongation in some patients. In particular, in certain populations (*e.g.*, patients with hepatic impairment and those taking inhibitors of CYP3A4 or the P-glycoprotein transporter), larger effects of ranolazine on the QT interval were seen or can be expected. Given that you have demonstrated effects on a symptom (*i.e.*, angina), and given the availability of other anti-anginal drugs that do not prolong the QT interval, there needs to be a clear reason to approve a therapy with what appears to be an additional, possibly life-threatening risk.

3) Adequate safety exposure. The present database has information on fewer than 1000 patients given relevant doses of ranolazine for at least one month, an exposure well below what is typically expected for a chronic treatment for a symptomatic claim.

To resolve the issue of potential testicular toxicity, additional animal data are needed, beginning with a more thorough review of the available histologic materials from the chronic animal toxicity studies. Depending on the outcome of that review, additional animal studies may be needed. Should a toxic effect of ranolazine on the testes be confirmed, the clinical consequences of this toxicity will need to be understood.

Regarding the effects of ranolazine on cardiac repolarization, we are not convinced by the available data that the effects of ranolazine on the QT interval would not lead to increased risk of arrhythmias at doses and in populations where it is likely to be used. To address this concern, you could provide data demonstrating that ranolazine has benefits that offset the concern arising from the effects on the QT interval. In patients with angina, this additional benefit could include showing efficacy in populations not adequately treated with maximally-tolerated or labeled doses of more than one class of approved anti-anginals. Such data should be obtained from randomized, prospectively-designed trials, exploring a broad range of doses of ranolazine, to be conducted following discussions with the Agency. Demonstration of a benefit on fixed clinical endpoints, such as myocardial infarction or death, also would obviously overcome concerns about effects on the QT interval. The available data suggest a smaller effect of ranolazine in women with angina; future clinical studies should further characterize this apparent gender difference. Finally, such a trial could satisfy the need for a larger safety database.

In addition, a retest date of eighteen months for the drug substance, and an expiration dating period of eighteen months for the drug product, will be granted based on the stability data provided.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Cardio-Renal Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please call Meg Pease-Fye, Regulatory Project Manager, at (301) 594-5312.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research